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Age-Specific Associations between Cardiac Vagal Activity and Functional Somatic Symptoms: A Population-Based Study

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Key Words
Autonomic nervous system · Heart rate variability · Cardiac vagal activity · Functional somatic symptoms

Abstract
Background: Functional somatic symptoms (FSS) are symptoms not explained by underlying organic pathology. It has frequently been suggested that dysfunction of the autonomic nervous system (ANS) contributes to the development of FSS. We hypothesized that decreased cardiac vagal activity is cross-sectionally and prospectively associated with the number of FSS in the general population. ***Methods:*** This study was performed in a population-based cohort of 774 adults (45.1% male, mean age ± SD 53.5 ± 10.7 years). Participants completed the somatization section of the Composite International Diagnostic Interview surveying the presence of 43 FSS. ANS function was assessed by spectral analysis of heart rate variability in the high-frequency band (HRV-HF), reflecting cardiac vagal activity. Follow-up measurements of HRV-HF and FSS were performed approximately 2 years later. ***Results:*** Linear regression analyses, with adjustments for gender, age, body mass index, anxiety, depression, smoking, alcohol use, and frequency of exercise, revealed an interaction of cardiac vagal activity with age: HRV-HF was negatively associated with FSS in adults ≤52 years of age ($\beta = -0.12$, $t = -2.37$, $p = 0.018$), but positively with FSS in adults aged >52 years ($\beta = 0.13$, $t = 2.51$, $p = 0.012$). Longitudinal analysis demonstrated a similar pattern. ***Conclusions:*** Decreased cardiac vagal activity is associated with a higher number of FSS in adults aged ≤52 years in the general population. The unexpected association between increased cardiac vagal activity and FSS in adults aged >52 years needs further exploration. The role of age should be acknowledged in future studies on ANS function in the etiology of FSS.

Introduction

It has been widely accepted that functional somatic symptoms (FSS), that is, physical complaints not explained by underlying organic pathology, have a multifactorial etiology with numerous contributing factors of biological, psychological, and social origin [1–4]. Although psychosocial stress is widely regarded as an important etiological factor [1], it is largely unknown how increased levels of psychosocial stress contribute to the experience of FSS. Dysfunction of the autonomic nervous system (ANS), a stress-responsive system, is an interesting underlying mechanism to consider [5].

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The ANS is influenced by acute, repetitive, and chronic psychosocial stress [6–8]. When the load of stressors in an individual is too large or when the ANS is chronically addressed, eventually ANS dysfunction may develop [9]. Given the vital role of the ANS in the regulation of bodily organs function, increased sympathetic activity or decreased parasympathetic activity may contribute to peripheral somatosensory arousal and experience of FSS [10–12]. Although ANS dysfunction seems a plausible mechanism to mediate the association between psychosocial stress and FSS, an alternative pathway is also possible. In this alternative pathway, ANS dysfunction may be a consequence or epiphenomenon of FSS, driven by factors such as medication use, psychiatric comorbidity, or lifestyle factors [13]. A widely used proxy for ANS function is heart rate variability (HRV), reflecting interbeat interval fluctuations in heart rate. HRV indices have been particularly used to assess cardiac vagal activity as reflected in the high-frequency band (HRV-HF) [14].

ANS function has never been studied in relation to FSS in the general population. However, cardiac vagal activity has been studied in patients with functional somatic disorders (FSD), which are clusters of related FSS. Examples of FSD are chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. A recent meta-analysis of those three FSD indicated statistically significant lower cardiac vagal activity in FSD patients compared to controls [15], with no apparent differences between chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. The validity of those summary estimates was, however, significantly limited by unexplained heterogeneity in the included studies. Furthermore, when taking the presence of potential publication bias into account, the difference in cardiac vagal activity between FSD patients and controls disappeared. These results suggest that some studies contrasting with the prevailing beliefs on lowered cardiac vagal activity in FSD have not been published. In addition, a structured review revealed substantial room for improvement in methodological quality, especially regarding adjustment for potential confounders. Furthermore, important potential moderators have not been taken into account. Only few studies have examined the associations of cardiac vagal activity and FSS according to gender [16, 17] and none has examined the associations according to age. Especially age may be an important moderator, as recently illustrated by a study on HRV and depression. While cardiac vagal activity generally decreases with increasing age [18], this study observed that cardiac vagal activity remained stable with increasing age in depressed patients but not in controls [19]. Finally, no longitudinal studies have been published exploring the issue whether ANS alterations precede development of FSS or FSD. All taken together, the current knowledge on the role of the ANS in FSS is inconclusive and requires further study.

The purpose of the present study was to investigate the role of ANS function in FSS in a large population-based cohort of adults, taking the role of potential confounders and moderators into account. We hypothesized that decreased cardiac vagal activity is cross-sectionally associated with FSS in the general population. In addition, we hypothesized that age moderated the association between cardiac vagal activity and FSS, in the sense that the association would be stronger in younger than in older adults. Additionally, we hypothesized that cardiac vagal activity is not differentially related to different bodily clusters of FSS. Furthermore, we hypothesized that decreased cardiac vagal activity predicts development of FSS in a 2-year follow-up period.

Subjects and Methods

Population

Our study was performed in a cohort derived from the Prevention of Renal and Vascular End-Stage Disease (PREVEND), a major population-based cohort study investigating microalbuminuria as a risk factor for renal and cardiovascular disease. The recruitment of participants for the PREVEND study has been extensively described elsewhere [20, 21]. The PREVEND study population (n = 8,592) was enriched for albuminuria, which was rectified in the current substudy in order to obtain a population-representative study sample. Research assistants handed over invitations to 2,554 subjects to participate in the current substudy for which additional psychiatric and psychosocial data were collected during two measurement waves. Baseline measurements in the 2001–2002 wave were completed by a total of 1,094 participants (43%), forming our study cohort. PREVEND participants who declined to participate in the current study did not significantly differ from those who did participate concerning gender, age, or neuroticism score [22]. Follow-up measurements in the 2003–2004 wave were completed by a total of 976 participants (89%). Dropout participants (n = 118) were older (mean age $\pm$ SD 56.6 $\pm$ 11.9 vs. 52.7 $\pm$ 11.2 years, $t = 3.66$, $p < 0.01$) and more often female (66 vs. 52%, $\chi^2 = 8.13$, $p < 0.01$), but did not differ significantly in baseline number of FSS or in neuroticism score. The study was approved by the local medical ethics committee. All subjects gave written consent to participate in the study.

Functional Somatic Symptoms

FSS were measured by the somatization section of the Composite International Diagnostic Interview (CIDI), as extensively described previously [21]. The CIDI has adequate test-retest reliability and validity [23]. Participants first completed the CIDI lifetime version measuring lifetime FSS. A total of 1,088 completed CIDIs were available at baseline. Two years later, participants

were reinterviewed and completed the CIDI 12-month version, in which the occurrence of the 43 symptoms in the previous year is surveyed; 964 completed CIDIs were available at follow-up. In our main analyses, we use the sum of all FSS in the CIDI 12-month version, henceforth defined as FSS. New-onset FSS were identified comparing the FSS reported in the CIDI 12-month version with those reported in the lifetime interview.

Additionally, we constructed bodily clusters of FSS, based on symptom clusters previously identified in a large study on the classification of FSS [24]. We defined a cardiopulmonary factor (chest pain and shortness of breath), a musculoskeletal factor (back pain, joint pain, pain in extremities, loss of touch or pain sensation, muscle weakness, and numbness or tingling sensations), a gastrointestinal factor (abdominal pain, nausea, diarrhea, feeling bloated or flatulence, and food intolerance), and a general symptoms factor (headache, trouble with balance and walking, dizziness). A dichotomous score for every bodily system symptom cluster was calculated (0 = no FSS in specific symptom cluster, 1 = one or more FSS in specific symptom cluster).

Cardiovascular Measures

Both at baseline and follow-up, HRV was measured with participants lying on a bench in the supine position in a quiet laboratory room, breathing spontaneously. Because of the circadian rhythm of cardiac vagal activity [25], timing of HRV measurements was standardized in the afternoon. Research assistants who measured HRV were blinded to our study hypotheses. There were no restrictions in eating, drinking, or smoking in the hours prior to the measurement. Participants were encouraged to relax and asked not to move or speak during data acquisition. A prerest period of 10 min in the supine position was applied before the HRV measurement started. A cuff was fixed around the middle phalanx of the third finger on the right hand. A Portapres device (FMS Finapres Medical Systems BV, Amsterdam, The Netherlands) continuously recorded heart rate during 10 min. Segments with a duration of approximately 300 s were selected for spectral analysis. In case there was no appropriate segment of 300 s, blocks of 60–300 s were selected [26]. Beat-to-beat variation measurements provided by the Finapres are almost interchangeable with electrocardiogram in the resting supine position [27]. Power spectral analysis of heart rate signals was performed with the CARSPAN software program [28]. The measurements were checked on stationarity and corrected for artifacts. Artifacts were eliminated and the resulting gaps were linearly interpolated. When containing more than 10% interpolated heart rate intervals or too many artifacts, the data were considered unstable and discarded. Participants for whom no reliable HRV measurement was available (<5% at both measurement waves) were comparable to participants with reliable HRV measurements regarding sex, age, and number of FSS. The high-frequency band (HRV-HF), defined at 0.15–0.40 Hz, is expressed in milliseconds squared and mainly reflects cardiac vagal activity [14, 26]. After natural logarithm (ln) transformation, HRV-HF values are expressed in ln (ms^2). Systolic blood pressure (BP) and diastolic BP were measured on two occasions in the supine position on the right arm every minute for 10 min with an automatic Dinamap XL model 9300 series monitor (Johnson-Johnson Medical Inc., Tampa, Fla., USA). BP (in mm Hg) was calculated as the mean of the last two measurements at both occasions.

Statistical Analysis

Analyses were performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, Ill., USA). Given the skewed distribution, the number of FSS and new-onset FSS were log-transformed (after transformation, skewness = 0.92, kurtosis = 0.14). Extreme values (>3 SD) of HRV-HF (n = 6 at baseline, n = 12 at follow-up) were excluded. We also excluded participants using antihypertensives (β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers assessed by self-report, n = 140 at baseline, n = 165 at follow-up), because these medications exert effects on HRV [29]. Multivariable linear regression analyses were used to assess the independent effect of HRV-HF on the number of FSS in both the cross-sectional and longitudinal analyses, and additionally on the new-onset FSS analysis (model 1). Interaction terms were created from the centered variables to avoid problems with multicollinearity (model 2). In case of statistically significant interactions, stratified analyses are presented (model 3). Standardized β values are given. Additionally, we applied multivariable logistic regression analyses to test the effect of HRV-HF on the odds of having FSS in a specific bodily system cluster. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented. All regression analyses were adjusted for gender, age, body mass index, anxiety and depressive disorder (DSM-IV diagnoses as assessed by CIDI), smoking, alcohol use, and frequency of exercise, since these may be responsible for variance in ANS function [30–34] and FSS [35–40]. Furthermore, interactions of both age and gender with HRV-HF (HRV-HF × age, HRV-HF × gender) were tested because we expected that the extent to which ANS dysfunction contributes to FSS might vary between age and gender groups [17, 41]. Longitudinal analyses were additionally adjusted for the number of lifetime FSS at baseline. All analyses were also performed after secondary exclusion of participants having self-reported cardiovascular disease or using antidepressant medication (nonselective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors) derived from the InterAction database containing pharmacy dispensing data [42]. All p values <0.05 were considered statistically significant.

Results

General Characteristics

Table 1 shows the general characteristics of our final study population (n = 774). The distribution of the total number of FSS is positively skewed; the median number of FSS was 1 (interquartile range 0–2). The most commonly reported FSS was headache (10.7%); other prevalent FSS were joint pain (10.6%) and back pain (9.4%).

Cross-Sectional Analysis of HRV-HF and FSS

Cross-sectional results from multivariable linear regression analyses are presented in table 2. In model 1, HRV-HF is not associated with the number of FSS. After entering interaction terms HRV-HF × age and HRV-HF × gender in model 2, a significant interaction between

Table 1. General characteristics of the study population

	All (n = 774)	Age ≤52 years (n = 403)	Age >52 years (n = 371)
Age (mean ± SD), years	53.5 ± 10.7	45.2 ± 4.8	62.5 ± 7.7
Female, %	54.9	56.1	53.6
Body mass index (mean ± SD)	25.9 ± 3.8	25.6 ± 3.9	26.3 ± 3.6
Smoking, %			
No smoking	79.6	75.7	83.8
1–5 cigarette(s)/day	2.7	3.2	2.2
6–10 cigarettes/day	4.3	5.0	3.5
11–15 cigarettes/day	6.2	7.9	4.3
16–20 cigarettes/day	5.0	5.5	4.6
>20 cigarettes/day	2.2	2.7	1.6
Alcohol use, %			
No alcohol use	20.2	17.6	22.9
1–4 unit(s)/month	16.4	15.1	17.8
2–7 units/week	33.2	39.7	26.1
1–3 unit(s)/day	27.5	25.3	29.9
>4 units/day	2.7	2.2	3.2
Frequency of exercise, %			
Not/hardly	49.5	43.4	58.4
Once per week	29.9	28.3	21.6
Twice or more per week	20.6	28.3	20.0
Antidepressant use, %	2.3	2.0	2.7
Depressive disorder (DSM-IV), %	6.7	7.7	5.7
Anxiety disorder (DSM-IV), %	5.7	6.4	4.7
Number of FSS (median)			
Number of FSS	1 (0–2)	1 (0–2)	1 (0–2)
Number of new-onset FSS	0 (0–1)	0 (0–1)	0 (0–1)
Number of lifetime FSS	3 (1–5)	3 (1–5)	2 (1–4)
Heart rate (mean ± SD), beats/min	69 ± 10	68 ± 10	69 ± 11
SBP (mean ± SD), mm Hg	122 ± 16	118 ± 13	127 ± 18
DBP (mean ± SD), mm Hg	72 ± 8	70 ± 8	73 ± 9
HRV-HF			
ms^2 (median)	466 (216–973)	645 (322–1,170)	314 (162–665)
ln ms^2 (mean ± SD)	6.15 ± 1.28	6.44 ± 1.22	5.85 ± 1.28

DBP = Diastolic blood pressure; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; SBP = systolic blood pressure. Figures in parentheses indicate interquartile ranges.

HRV-HF and age emerges, indicating that the association between HRV-HF and the number of FSS changes with increasing age. Model 3 presents a stratified analysis based on a median split of the modifying variable age. This stratification reveals that HRV-HF is inversely and significantly associated with FSS in adults aged ≤52 years ($\beta = -0.12$, $t = -2.37$, $p = 0.018$), whereas HRV-HF is positively and significantly associated with FSS in adults aged >52 years ($\beta = 0.13$, $t = 2.51$, $p = 0.012$). Additionally, we calculated the coefficients of HRV-HF in explaining the number of FSS in 5 age categories, demonstrating that this interaction effect is linear (age <45 years, $\beta = -0.19$, $t = -2.24$, $p = 0.027$; age 45–50 years, $\beta = -0.07$, $t = -0.96$, $p = 0.339$; age 51–55 years, $\beta = 0.00$, $t = 0.01$, $p = 0.996$; age 56–60 years, $\beta = 0.09$, $t = 0.99$, $p = 0.324$; age >60 years, $\beta = 0.15$, $t = 2.08$, $p = 0.039$). In table 1, the general characteristics of the two age groups based on the median split are shown.

Cross-Sectional Analysis of HRV-HF and Bodily Clusters of FSS

Next, we examined whether the association between HRV-HF and FSS was the same in different bodily clusters. Due to the low number of participants having FSS

Table 2. Coefficients from multivariable linear regression models predicting the number of FSS out of HRV-HF and possible confounders: cross-sectional analysis

	Model 1		Model 2		Model 3			
	all participants (n = 774)		all participants (n = 774)		age ≤52 years (n = 403)		age >52 years (n = 371)	
	β	p value	β	p value	β	p value	β	p value
HRV-HF	0.00	0.923	−0.02	0.620	−0.11	0.018*	0.13	0.012*
Female gender	0.18	<0.001*	0.19	<0.001*	0.19	<0.001*	0.22	<0.001*
Age	0.02	0.592	0.02	0.557	0.03	0.512	0.06	0.271
Body mass index	0.07	0.051	0.06	0.073	0.11	0.024*	0.00	0.993
Anxiety	0.21	<0.001*	0.21	<0.001*	0.18	<0.001*	0.31	<0.001*
Depression	0.11	0.003*	0.11	0.004*	0.19	<0.001*	−0.03	0.600
Smoking	0.07	0.052	0.07	0.066	0.06	0.208	0.04	0.439
Alcohol	−0.09	0.015*	−0.08	0.024*	−0.19	<0.001*	0.06	0.259
Frequency of exercise	−0.01	0.737	−0.01	0.853	−0.02	0.691	−0.03	0.564
HRV-HF × age			0.10	0.004*				
HRV-HF × gender			−0.04	0.286				
R^2	0.14		0.15		0.22		0.14	

* $p < 0.05$. Model 3 is based on a median split of the moderating variable age.

in the cardiorespiratory bodily cluster (n = 41), this cluster was excluded for multivariable logistic regression. Similar to the cross-sectional analyses with the total number of FSS, for all clusters borderline statistically significant HRV-HF × age interaction effects were observed. The OR for HRV-HF × age for the 3 bodily symptom clusters followed the same pattern and magnitude: HRV-HF × age predicted FSS in the musculoskeletal factor (OR = 1.18, 95% CI = 0.98–1.42, z = 3.06, p = 0.080), gastrointestinal factor (OR = 1.21, 95% CI = 0.96–1.54, z = 2.58, p = 0.108), and general symptoms factor (OR = 1.22, 95% CI = 0.99–1.51, z = 3.32, p = 0.069).

Longitudinal Analysis of HRV-HF and FSS

In the longitudinal analysis, a similar pattern as found in the cross-sectional analysis emerged for the relation between HRV-HF and FSS (see table 3 for an overview). In model 1, HRV-HF at baseline does not predict the number of FSS at follow-up approximately 2 years later. In model 2, the interaction term HRV-HF × age is statistically significant (β = 0.07, t = 1.97, p = 0.049). After stratification in two age groups based on a median split, the β values follow the same pattern as in the cross-sectional analyses, however, HRV-HF does not significantly predict FSS in any of those subgroups. Additionally, when only considering new-onset FSS, i.e. FSS that were only reported in the 12-month interview performed at follow-up but not in the lifetime interview performed at baseline, essentially the same pattern emerged (data not shown).

All analyses were also performed after secondary exclusion of participants having cardiovascular disease or using antidepressant medication. These secondary analyses did not essentially change the results; therefore, only results of the total sample are shown for maximal generalizability.

Discussion

The aim of this study was to investigate the relation between ANS dysfunction and FSS in a general population-based cohort. As hypothesized, lower HRV-HF, which indicates decreased cardiac vagal activity, was associated with the number of FSS in adults aged ≤52 years. In contrast, in adults aged >52 years, higher HRV-HF was associated with the number of FSS. The same pattern, although not statistically significant in all analyses, emerged in the prospective part of our study when predicting FSS at 2-year follow-up.

This is the first study to report on the relationship between ANS function and FSS in a population-based cohort adjusted for a large range of confounders. In adults

Table 3. Coefficients from multivariable linear regression models predicting the number of FSS out of HRV-HF and possible confounders: longitudinal analysis

	Model 1		Model 2		Model 3			
	all participants (n = 700)		all participants (n = 700)		age ≤52 years (n = 354)		age >52 years (n = 346)	
	β	p value	β	p value	β	p value	β	p value
HRV-HF	0.03	0.413	0.02	0.640	–0.02	0.704	0.07	0.143
Female gender	0.07	0.052	0.07	0.033*	0.10	0.049*	0.05	0.332
Age	0.09	0.006*	0.09	0.007*	0.07	0.158	0.09	0.070
Body mass index	0.04	0.240	0.04	0.232	0.08	0.100	0.01	0.845
Anxiety	0.09	0.014*	0.09	0.014*	0.11	0.028*	0.05	0.308
Depression	0.05	0.143	0.05	0.138	0.15	0.003*	–0.07	0.160
Smoking	0.05	0.143	0.05	0.163	0.04	0.358	0.04	0.450
Alcohol	–0.02	0.527	–0.02	0.555	–0.09	0.052	0.06	0.233
Frequency of exercise	0.00	0.965	0.00	0.967	–0.04	0.447	0.04	0.434
Lifetime FSS	0.50	<0.001*	0.50	<0.001*	0.43	<0.001*	0.56	<0.001*
HRV-HF × age			0.07	0.049*				
HRV-HF × gender			0.03	0.375				
R^2	0.32		0.32		0.35		0.34	

* $p < 0.05$. Model 3 is based on a median split of the moderating variable age.

aged ≤52 years, our results are in agreement with previous findings of lower HRV-HF at rest in patients with FSD in a meta-analysis [15]. Although the reliability of the summary estimate in this meta-analysis was affected by poor quality of underlying studies, heterogeneity, and potential publication bias, the present study supports the finding of lower HRV-HF in persons with FSS. This association was the same for males and females. As hypothesized, we have demonstrated that general, musculoskeletal, and gastrointestinal FSS bodily clusters share a comparable association with HRV-HF.

Unexpectedly, as high cardiac vagal activity should protect against the sensation of FSS according to our hypothesis, we have demonstrated a significant association between higher cardiac vagal activity and the number of FSS in adults aged >52 years, which remained after exclusion of participants with cardiovascular disease. Given the current lack of similar research in this age group, we can only speculate about reasons for the positive association between HRV-HF and FSS in adults >52 years old.

First, etiological factors in the development of FSS may differ between younger and older persons [43], which may also apply to the role of stress-responsive systems. In the current study, explained variance in FSS is 20% in adults aged ≤52 years in contrast to only 14% in adults >52 years of age. For example, in keeping with our results, it has been found that depressive disorder is not associated with FSS in older adults [44]. However, age differences in etiological factors do not specifically explain the *positive* direction of the association with HRV-HF and FSS in adults aged >52 years.

Second, HRV-HF decreases with increasing age and has been associated with several diseases of aging, including obesity, diabetes mellitus, and hypertension [45], making it difficult to distinguish low HRV related to disease from normal aging. Also, variance in HRV-HF increases and reliability decreases with increasing age [46]. This may indicate that high HRV values reflect different physiological processes in younger persons than in older persons [47]. Indeed, it has been reported that not only low HRV, as repeatedly found in previous population-based cohort studies, but also high HRV is a prognostic factor for cardiovascular mortality in the elderly [48]. Authors ascribe this remarkable finding to an increased prevalence of sinus node dysfunction causing higher HRV. However, excluding participants with cardiovascular comorbidity from our study sample did not essentially change the results. An unanticipated interaction between age and HRV-HF in psychophysiological research has been shown before, in a study examining HRV-HF

and depression in the elderly. As expected, increasing age was associated with decreased HRV-HF in healthy controls, however, the depressed group did not show an association between age and HRV-HF [19]. In this study, inspection of regression lines suggests that between-group differences might be evident before age 60, but not thereafter. This cutoff seems to be in line with the age-associated differences in the association between HRV-HF and FSS in the present study.

Third, sensitivity to painful stimuli correlates inversely with BP levels, possibly due to baroreflex-mediated inhibition of pain transmission at both spinal and supraspinal levels, a process known as hypertension-associated hypalgesia [49]. The prevalence of hypertension, which is characterized by lower cardiac vagal activity, is higher in older adults [29]. Therefore, hypertension-associated hypalgesia would be consistent with our finding of a positive association between HRV-HF and FSS in adults aged >52 years. However, only a minority of the FSS concern pain symptoms. In addition, post hoc tests taking BP into account as a possible confounder in the current study did not significantly attenuate the positive association between HRV-HF and FSS in adults aged >52 years.

All taken together, a comprehensive explanation for the association between increased HRV-HF and FSS in older age groups appears not readily available. This intriguing finding warrants further research.

The current study is the first to present prospective data on ANS function and FSS. It can be argued that alterations in cardiac vagal activity do not cause FSS, but are instead a consequence or epiphenomenon. In that case, ANS alterations are due to lifestyle factors such as physical inactivity, smoking and alcohol use, medication use, or psychiatric comorbidity [13]. However, HRV-HF was still independently associated with FSS in our analyses taking those factors into account. Longitudinal analyses, examining whether lowered cardiac vagal activity predicts development of FSS, yielded essentially the same results as the cross-sectional part of the study. Of note, prospective associations were weaker and not always statistically significant. As results in our longitudinal analyses are not conclusive, this association may be better studied in populations at risk for FSS and FSD.

Some limitations of this study should be taken into account.

First, the number of FSS in the CIDI was measured by retrospective self-report. Nevertheless, we are confident that we were able to identify FSS using the CIDI, since associations with important characteristics like gender, depression, and anxiety were similar to previous studies on the prevalence of FSS in the general population [50] and in primary care [51] in which a medical doctor was directly involved.

Second, three remarks regarding our measurement of HRV should be taken into account. Although recommended as a quality criterion [15], we did not give restrictions in eating, drinking or smoking in the hours before the HRV measurements. However, we do not think this has influenced our results substantially, since we adjusted the analyses for smoking and alcohol use. Furthermore, we used BP fluctuations as determined by the Finapres finger cuff to detect the occurrence of a heart beat. Although the distal pulse wave is almost interchangeable with an electrocardiogram [27], it may be argued that the use of an electrocardiogram may be preferable, especially when participants with different ages are included as arterial stiffness and thereby pulse transit time is influenced by age. However, it has been shown that pulse pressure is not independently associated with HRV after controlling for age and gender. Therefore, we do not think that measuring heart rate peripherally has influenced our findings [52]. Third, we did not measure respiratory rate and depth, while it has been recommended that respiration frequency needs to be monitored and adjusted for to generate an accurate measure of HRV-HF. However, this requirement seems particularly relevant when studying within-subject HRV measurements [53], whereas correction or control procedures are discouraged in between-subject design such as in our study, since HRV-HF seems not dependent on respiration frequency under baseline conditions [54].

Finally, we did not measure some factors that may further characterize the type of somatization, such as precipitating psychological events or demoralization [5], and may influence its association with cardiac vagal activity.

Among the strengths of this study are the large sample size and the extensive data collection allowing for adjustment of potential confounders and detecting gender- and age-dependent effects, which has been an area of weakness in previous research. In addition, our longitudinal data on ANS dysfunction in relation to FSS are unique and enabled us to study the direction of effects.

In conclusion, decreased cardiac vagal activity appeared to be associated with FSS in adults aged ≤52 years in the general population. Unexpectedly, higher cardiac vagal activity was associated with FSS in adults aged >52 years, a finding that needs replication and better understanding. Further prospective studies investigating the

role of the ANS in FSS, acknowledging the role of age, are required to make a next step in clarifying the role of ANS dysfunction in the etiology of FSS.

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Conflict of Interest

None of the authors report any biomedical financial interest or other potential conflict of interest.

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